MRI key findings and frequency of neurogenic tumors of soft tissue in a 4 years cohort.

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Learning objectives

Make an exhaustive review of literature reference about neurogenic tumors of soft tissue, trying to find key features in each variety. Summarize this findings and compare them with features found in the studies of our 4 year cohort.
Background

OVERVIEW OF NEUROGENIC TUMORS

Neurogenic Tumors of soft tissues or Nerve sheath tumors are lesions that arise from the displaying differentiation along the lines of the various elements of the nerve sheath. [1(Gilchrist 2014)]

Symptoms and signs of peripheral nerve tumors are caused by direct nerve invasion, involvement of surrounding tissues, or mass effect. There are no specific clinical presentations or even suggestive of a particular nerve tumor. The duration and progression of symptoms or signs is important as most benign tumors have a longer duration and a slow rate of progression, while malignant tumors tend to progress rapidly in size, amount of pain, and neurologic deficit. It is important a carefully assessment of family history to dismiss an underlying neuro genetic disorder, such as neurofibromatosis. [1(Gilchrist 2014)]

Imaging is the most valuable tool for evaluation of peripheral nerve tumors. MRI is the most helpful imaging modality, especially showing the presence of a mass, determining if it is intrinsic or extrinsic to the nerve, and evaluating involvement of adjacent structures. It is less helpful in determining the pathology of the tumor as there are no pathognomonic signal characteristics for any type of tumor. Although not definitive, MRI can be helpful in determining the malignant nature of a tumor. Rapid expansion of a known tumor, inhomogeneous enhancement, hemorrhage, necrosis, and heterogeneous signal suggest, but do not confirm, the presence of a malignant nerve sheath tumor. Large tumors exceeding 5 cm, ill-defined margins, invasion of fat planes, and edema around the tumor all raise the possibility of malignancy. CT scan is not the best imaging method, many tumors have signal densities similar to muscle and so are not well defined. However, CT can be useful in demonstrating bony remodeling adjacent to the tumor. PET-CT has shown some promise in distinguishing malignant peripheral nerve sheath tumors (MPNSTs) from benign tumors.[1(Gilchrist 2014)] PET CT, which allows visualization of glucose metabolism by cells, has been reasonably successful in identifying malignant change in plexiform neurofibromas and may give some information of the grade of the lesion. [2(Goldblum 2014)]. Table 1 on page 7

CLASSIFICATION:

Table 2 on page 7

BENIGN NEUROGENIC TUMORS

BENIGN NON-NEOPLASTIC NERVE TUMORS
The category includes neuroma, ganglion cyst, intraneural heterotopic ossification, sarcoid granuloma, inflammatory pseudotumor of nerve, leprosy, hypertrophic neuropathy, lipofibromatous hamartoma, and neuromuscular choristoma. [1(Gilchrist 2014)]

**Neuromas** belong to a class of tumors best called reactive. *Traumatic neuromas* occur after nerve injury causing interrupted axons (neurotmesis). Regenerating axons result in a mass of disorganized axons. Neuromas tend to be small and firm in texture. *Morton's neuroma* are typically located between the metatarsals of the third and fourth toes or at the bifurcation of the fourth plantar digital nerve. Histologically the lesions look like a traumatic neuroma grossly. Clinical manifestations can include pain and tenderness, but similar lesions are common in patients who are asymptomatic. It is more common in middle-aged women, associated with the use of high heels. MRI is highly sensitive and specific for the diagnosis, presenting signal isointense to muscle on T1-weighted sequences and low signal to fat on T2 weighted images. *Fig. 1* on page 8

**Solitary neuromas** are small, firm, nonpigmented, painless nodules found in proximity to mucocutaneous junctions, most frequently in the face. *Mucosal neuromas* are associated with multiple endocrine neoplasia type IIb and could be present as diffusely enlarged lips, tongue nodules, and thickened eyelids, either diffusely or nodular, usually in the first or second decade. [1(Gilchrist 2014)]

**BENIGN NEOPLASTIC NERVE TUMORS**

Schwannomas are slightly less common than neurofibromas, together these lesions are about 10% of all benign soft tissue tumors.

**Schwannoma** is a slow-growing tumor arising from the outer sheath of a peripheral nerve. Typically is a solitary encapsulated lesion that may be cystic when it is 3 to 4 cm in diameter. Any nerve may be involved [4(Toy 2012)]. The tumor is typically eccentric to the nerve fibers, which may be diagnosed prospectively, especially if proximal and distal nerve fibers are visualized on the MRI. It may be difficult to recognize the associated nerve fiber when tumors arise from small nerve branches. The flexor surfaces of the extremities (particularly the ulnar and peroneal nerves), mediastinum, retroperitoneum, head, and neck are the most common sites. Long-standing and large lesions, known as giant ancient schwannomas, may have cystic changes, calcification, hemorrhage, and fibrosis that may be mistaken for more aggressive tumors on imaging. [3(Ilaslan 2014)] Malignant degeneration has been described but rarely occurs. [4(Toy 2012)] *Fig. 2* on page 9 *Fig. 3* on page 10

**Neurofibromas** are also slow-growing lesions with a centrally entering and exiting nerve, which gives a fusiform shape to the tumor. Unlike schwannomas, neurofibromas often lack a capsule, and the tumor tissue cannot be separated from normal nerve fibers on
Neurofibromas are usually seen in the second and third decades of life. [3(Ilaslan 2014)]. Fig. 4 on page 11

Neurofibromas are typically associated with neurofibromatosis type 1 (NF1). Can occur in anywhere in the body, including skin, subcutaneous tissues, and viscera. Fig. 5 on page 12. There are three types of neurofibromas: localized, diffuse, and plexiform. All three types may be associated with NF1. Localized neurofibroma is the most common type seen with NF1. Although less common, plexiform neurofibromas are essentially pathognomonic of NF1. Plexiform neurofibromas usually develop during childhood and adolescence and can precede the appearance of cutaneous neurofibromas. Plexiform neurofibromas may be associated with massive and disfiguring enlargement of an extremity called elephantiasis neuromatosa, which may be associated with bony hypertrophy. [3(Ilaslan 2014)] Fig. 6 on page 12

Schwannomas and neurofibromas share many imaging features on an MRI.

1. Both present as well-defined, often elongated masses that rarely exceed 5 cm in diameter.
2. Continuity with a nerve, the most helpful diagnostic MRI feature, is usually evident on images of lesions arising from larger nerves.
3. Differentiation of schwannomas and neurofibromas based on the position of the tumor relative to the nerve (eccentric versus central) is often difficult, especially when smaller nerves are involved.
4. Intramuscular neurogenic tumors may be surrounded by a thin rim of fat; this creates the split-fat sign on T1-weighted MR images, especially along the long axis of the extremity as a result of slow growth over a long term.
5. Most benign neurogenic tumors are isointense or slightly hyperintense to muscle on T1-weighted images and are markedly hyperintense to fat with a variable degree of heterogeneity on T2-weighted images.
6. On fluid-sensitive sequences, these tumors may exhibit high signal intensity in the periphery and low-to-intermediate signal intensity centrally. This appearance is likely caused by myxoid material peripherally and fibrous tissue centrally, called target sign. Although the target sign was initially thought to be pathognomonic of neurofibromas, it has also been observed in schwannomas and even in MPNSTs.
7. Multiple small ring-like structures, fascicular sign, within the neurogenic tumors may be visualized on an MRI, representing the fascicular bundles. [3(Ilaslan 2014)]

MALIGNANT NERVE TUMORS

MPNSTs arising from or displaying differentiation along the lines of the various elements of the nerve sheath (e.g., Schwann cell, perineural cell, fibroblast) are collectively
referred to as malignant peripheral nerve sheath tumors (MPNSTs). Their diagnosis have traditionally been one of the most difficult and elusive among soft tissue tumors in the past because of a lack of standardized diagnostic criteria. Even today, there are no specific biomarkers that can be used to establish the diagnosis with certainty. Although there is a general agreement that a sarcoma can usually be considered an MPNST if it arises from a peripheral nerve or a neurofibroma.

A sarcoma is assumed to be an MPNST if one of three criteria can be met: (1) arises from a peripheral nerve and shows no aberrant or heterologous line of differentiation; (2) it arises from a preexisting benign nerve sheath tumor, usually a neurofibroma; or (3) the tumor displays a constellation of histologic features that are seen in tumors arising in the foregoing situations and are considered typical of malignant Schwann cell tumors. [2(Goldblum 2014)]

About 25% of patients with this tumor have neurofibromatosis. Approximately 5% of patients who have neurofibromatosis develop malignant change in a neurofibroma, and pain should alert the clinician to the possibility of transformation. It originally was thought that patients with neurofibromatosis had a worse prognosis than other patients with malignant peripheral nerve sheath tumor. These tumors typically arise along a major peripheral nerve in adults 30 to 50 years old. Patients with NF1 develop sarcomas usually after a relatively long latency (10 to 20 years), and, in some cases, the MPNSTs are multiple. MPNSTs in childhood are recognized but infrequent. In sporadic cases, the gender ratio is roughly equal. The exact mechanism of malignant transformation or tumor progression in NF1 is not fully understood but involves a multistep process in which genes other than the NF1 gene also participate. [2(Goldblum 2014)]

At the initial examination, most patients have a painless mass. Some patients complain of pain in the distribution of the involved nerve, and the complaint of pain is more prevalent in those with neurofibromatosis type 1. Microscopic diagnosis of early malignant change in a neurofibroma may be difficult. The tumors have a similar microscopic appearance as a fibrosarcoma; however, the spindle cells tend to have irregular contours. Local recurrence is high in some series because the tumor can extend along the perineurium of the involved nerve for some distance. Overall 5-year survival is approximately 50%. [4(Toy 2012)]

In its classic form, an MPNST arises as a large fusiform or eccentric mass in a major nerve. Thickening of the nerve proximally and distally to the main mass usually indicates spread of the neoplasm along the epineurium and perineurium. In NF1 patients, MPNST may develop in a preexisting neurofibroma. Most of these lesions are deeply situated; only rare ones arise from superficial neurofibromas. Regardless of the clinical setting, the gross appearance of the MPNST is essentially similar to that of other soft tissue sarcomas. Fig. 7 on page 13 It is usually large, averaging more than 5#cm in diameter and has a fleshy, opaque, white-tan surface marked by areas of secondary hemorrhage and necrosis. This appearance contrasts with the white mucoid appearance of the typical neurofibroma.[2(Goldblum 2014)] Fig. 8 on page 14
<table>
<thead>
<tr>
<th>TUMOR</th>
<th>AGE</th>
<th>LOCALIZATION</th>
<th>GENDER PREDOMINANCE</th>
<th>CLINICAL ASPECTS</th>
<th>IMAGING FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORTON NEUROMA</td>
<td>Middle-aged individuals</td>
<td>Typically between the metatarsals of the third and fourth toes</td>
<td>Many times more common in women than men</td>
<td>Pain and tenderness-asymptomatic</td>
<td>MRI T1 - typically low to iso signal. T2 - typically low signal but can sometimes be intermediate in signal T1 C+ (Gd) - tends to show intense enhancement</td>
</tr>
<tr>
<td>MALIGNANT PERIPHERAL NERVE SHEATH TUMOR</td>
<td>2nd–5th decades</td>
<td>Large peripheral nerves (sciatic, brachial plexus, sacral plexus)</td>
<td>Up to 50% in patients with neurofibromatosis type 1</td>
<td>Enlarging, palpable mass. Pain variable, muscle weakness, paresthesias</td>
<td>MRI— fusiform shape, longitudinal orientation in direction of nerve; invasion of fat planes, heterogeneity, ill-defined margins, surrounding edema</td>
</tr>
</tbody>
</table>

**Table 1:** Features of Nerve Sheath Tumors

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## Classification of Nerve Sheath Tumor

### Benign Nerve Sheath Tumors

- **Benign Non-neoplastic Nerve Tumors**
  - Neuromas
  - Traumatic neuromas
  - Morton’s neuroma
  - Solitary neuromas
  - Mucosal neuromas

- **Benign Neoplastic Nerve Tumors**
  - Schwannomas
  - Neurofibromas
    - Localized
    - Diffuse
    - Plexiform

### Malignant Nerve Sheath Tumors

- Malignant Peripheral Nerve Sheath Tumor (MPNSTs)

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**Table 2:** Classification of Nerve Sheath Tumor

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Fig. 1: 53 y/o woman. Morton's neuroma in the third intermetatarsal space in the left foot. (a) MRI coronal T1 sequence shows isointense, well defined lesion. (b) axial T1-weighted, isointense to the muscle mass with hourglass morphology. (c) T2-weighted sequence fat-sat, lesion with intermediate, heterogeneous signal (arrow).

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Fig. 2: 34 y/o male. Right forearm Schwannoma. (a) MRI axial T1, there is an isointense well-defined mass(arrows). (b) Axial T2, the lesion is hyperintense and heterogeneous. (c) Sagittal T1 + Gadolinium, fusiform mass with heterogeneous enhancement and hypointense central area,"target sign"(arrow).(d) Coronal DP fat-sat there is a fusiform hyperintense and heterogeneous lesion in continuity with a neural structure(arrows)

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**Fig. 3:** 34 y/o male. Schwannoma in the right hand. (a) Coronal T1 + Gadolinium, there is a lesion with heterogeneous enhancement and hypointense center: Target Sign. (arrow) (b) MRI axial T1-weighted sequence, there is an isointense mass with hourglass morphology. (c) Axial T2 sequence, hyperintense and heterogeneous mass.

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**Fig. 4:** 61 y/o female. Neurofibroma, in the third intermetatarsal space in the right foot. a) MRI axial T1-weighted sequence, there is a multi-lobed mass with hourglass morphology,
isointense to muscle. b) Axial T2-weighted sequence, the lesion is hyperintense and heterogeneous. (c) Axial T2 fat sat sequence, high signal lesion. (d) Coronal DP weighted, well defined hyperintense lesion.

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**Fig. 5:** Multiple neurofibromas in a patient with a history of neurofibromatosis. (a) MRI sagittal T1-weighted there are two masses continuously with the nerve sheath, isointenses to muscle. (b) T2-weighted sequence fat sat, the lesions are heterogeneous and hyperintense. (c,d) axial T1 without and with Gadolinium, there are hyperintense heterogeneous lesions (d)Lesions shown an heterogeneous enhancement.

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**Fig. 6:** 5 y/o female with Neurofibromatosis type 1 and neck mass, plexiform neuroma. MRI coronal and axial imaging T2 weighted. There is a plexiform neuroma seen throughout the neck. The diffuse neurofibroma are also seen distributed throughout the prevertebral and paravertebral spaces greater on the right.

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**Fig. 7:** 56 y/o female. MPNST in the left forearm. (a,c). MRI sagittal and axial T1-weighted, there is a well defined lesion, isointense to the muscle. (b,d) MRI DP weighted + fat sat, hyperintense lesion, with fusiform morphology. Despite of the benign imaging features, the lesion have had histological confirmation of malignity.
**Fig. 8:** 62 y/o female. MPNST in abdominal wall with bone and lung metastases. 
a) Abdominal US, there is an hypoechoic, well-defined, homogeneous lesion in subcutaneous tissue. 
b) Impairment of right humerus with associated soft tissue mass. 
c) CT chest multiple metastatic nodules.
Findings and procedure details

From our database of 1590 soft tissue tumors with histological confirmation, we focus on neurogenic tumor, reviewing the MRI findings, morphological features and frequency. We compared our findings with reference literature and we made conclusions.

In our cohort there were 40 neurogenic tumors, which represent 2.5% of all soft tissue tumors. We found a slight predominance in female (22/18). The average age was 49 years old. 97.5% were benign. The most frequent was Morton's neuroma, followed by schwannoma and neurofibroma. Malignant tumors were less common, being only 2.5%.

Fig. 9 on page 17 Table 3 on page 17

- **Morton's neuroma**

In our series, is the most common benign tumor corresponding to 50% of all tumors of neurogenic.
The average age was 53 years, most common in women, (15) 75%.

From 20 patients with histological diagnosis of Morton's neuroma, only 9 had MRI. The study protocol includes at least T1-, T2 and T2 with fat suppression. All patients had lesions with isointense signal intensity on T1 and hypointense on T2-weighted sequences. In fat sat sequences there was great variability, without defining a characteristic pattern.

- **Schwannomas**

Schwannomas were second in frequency, 35% (N = 14). The average age was 43 years, being more common in men than in women, unlike described in the literature, with a total of 10 men, which corresponds to 71%. 64% (N = 9) was located in the appendicular skeleton.

On the MRI lesions schown isointense signal on T1, heterogeneous hyperintensity on T2-weighted sequences and heterogeneous enhancement after gadolinium administration.

- **Neurofibromas**

They were the third benign tumor more frequently, 12.5% (N = 5). The average age was 52 years. The frequency by gender were similar. There was no a definite distribution pattern. MRI presented as hypointense signal on T1, hyperintense on T2 and heterogeneous after administration of gadolinium.

- **Malignant Peripheral Nerve Sheath Tumor (MPNSTs)**
The least common tumors were MPNSTs, corresponding to only 2.5% (N = 1). Was a 62 year old woman with a tumor in the right abdominal wall. No MR images were found. We had only an abdominal ultrasound study four years before diagnosis, in which a mass is evident in the right abdominal wall at the height of the iliac fossa, rounded morphology, hypoechoic, well-defined edges. Subsequently the mass presented rapid growth in months with lung, bone and soft tissue metastases.
**Fig. 9:** Frequency of Neurogenic Tumors in a cohort of four years

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### Features Benign Neurogenic Tumors of Soft Tissue

<table>
<thead>
<tr>
<th></th>
<th>Morton's Neuroma</th>
<th>Schwannoma</th>
<th>Neurofibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate by Gender</strong></td>
<td>15 Female (75%)</td>
<td>4 Female (29%)</td>
<td>2 Female (40%)</td>
</tr>
<tr>
<td></td>
<td>5 Male (25%)</td>
<td>10 Male (71%)</td>
<td>3 Male (60%)</td>
</tr>
<tr>
<td><strong>Average Age (y/o)</strong></td>
<td>53</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td><strong>Signal Features MRI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Isointense (100%)</td>
<td>Isointense</td>
<td>Isointense</td>
</tr>
<tr>
<td>T2</td>
<td>Hypointense (100%)</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperintense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>STIR</td>
<td>Variable Signal</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>T1 + C (Gad)</td>
<td>-</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement</td>
<td>Enhancement</td>
</tr>
</tbody>
</table>
**Table 3:** Features Neurogenic Tumors of Soft Tissue in our cohort

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Conclusion

In our series, tumors of neurogenic lineage meet the same characteristics as reflected in literature, in terms of frequency, location and findings on MRI image.

1. They are rare, corresponding to only 2.5% of soft tissue tumors.
2. Most are benign (97.5%)
3. The frequency of malignant peripheral nerve sheath is low, being only 2.5%.
4. MRI findings do not show an specific pattern, being difficult to differentiate between benign and malignant histological types.